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Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To determine the clinical manifestations, risk factors, and maternal and perinatal outcomes in pregnant and recently pregnant women with suspected or confirmed coronavirus disease 2019 (covid-19).

DESIGN

Living systematic review and meta-analysis.

DATA SOURCES

Medline, Embase, Cochrane database, WHO COVID-19 database, China National Knowledge Infrastructure (CNKI), and Wanfang databases from 1 December 2019 to 26 June 2020, along with preprint servers, social media, and reference lists.

STUDY SELECTION

Cohort studies reporting the rates, clinical manifestations (symptoms, laboratory and radiological findings), risk factors, and maternal and perinatal outcomes in pregnant and recently pregnant women with suspected or confirmed covid-19.

DATA EXTRACTION

At least two researchers independently extracted the data and assessed study quality. Random effects meta-analysis was performed, with estimates pooled as odds ratios and proportions with 95% confidence intervals. All analyses will be updated regularly.

RESULTS

77 studies were included. Overall, 10% (95% confidence interval 7% to14%; 28 studies, 11 432 women) of pregnant and recently pregnant women attending or admitted to hospital for any reason were diagnosed as having suspected or confirmed covid-19. The most common clinical manifestations of covid-19 in pregnancy were fever (40%) and cough (39%). Compared with non-pregnant women of reproductive age, pregnant and recently pregnant women with covid-19 were less likely to report symptoms of fever (odds ratio 0.43, 95% confidence interval 0.22 to 0.85; I^2=74%; 5 studies; 80 521 women) and myalgia (0.48, 0.45 to 0.51; I^2=0%; 3 studies; 80 409 women) and were more likely to need admission to an intensive care unit (1.62, 1.33 to 1.96; I^2=0%) and invasive ventilation (1.88, 1.36 to 2.60; I^2=0%; 4 studies, 91 606 women). 73 pregnant women (0.1%, 26 studies, 11 580 women) with confirmed covid-19 died from any cause. Increased maternal age (1.78, 1.25 to 2.55; I^2=9%; 4 studies; 1058 women), high body mass index (2.38, 1.67 to 3.39; I^2=0%; 3 studies; 877 women), chronic hypertension (2.0, 1.14 to 3.48; I^2=0%; 2 studies; 858 women), and pre-existing diabetes (2.51, 1.31 to 4.80; I^2=12%; 2 studies; 858 women) were associated with severe covid-19 in pregnancy. Pre-existing maternal comorbidity was a risk factor for admission to an intensive care unit (4.21, 1.06 to 16.72; I^2=0%; 2 studies; 320 women) and invasive ventilation (4.48, 1.40 to 14.37; I^2=0%; 2 studies; 313 women). Spontaneous preterm birth rate was 6% (95% confidence interval 3% to 9%; I^2=55%; 10 studies; 870 women) in women with covid-19. The odds of any preterm birth (3.01, 95% confidence interval 1.16 to 7.85; I^2=1%; 2 studies; 339 women) was high in pregnant women with covid-19 compared with those without the disease. A quarter of all neonates born to mothers with covid-19 were admitted to the neonatal unit (25%) and were at increased risk of admission (odds ratio 3.13, 95% confidence interval 2.05 to 4.78, I^2=not estimable; 1 study, 1121 neonates) than those born to mothers without covid-19.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Pregnant women are considered to be a high risk group for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the potential adverse effects of the virus on maternal and perinatal outcomes are of concern

In non-pregnant populations admitted to hospital with coronavirus disease 2019 (covid-19) the most common symptoms are fever, cough, and dyspnoea, reported in more than two thirds of individuals

Advancing age, high body mass index, non-white ethnicity, and pre-existing comorbidities are risk factors for severe covid-19 in the general population

WHAT THIS STUDY ADDS

Pregnant and recently pregnant women with covid-19 diagnosed in hospital are less likely to manifest symptoms of fever and myalgia than non-pregnant women of reproductive age and might be at increased risk of admission to an intensive care unit

Risk factors for severe covid-19 in pregnancy include increasing maternal age, high body mass index, and pre-existing comorbidities

Pregnant women with covid-19 are more likely to experience preterm birth and their neonates are more likely to be admitted to a neonatal unit

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CONCLUSION

Pregnant and recently pregnant women are less likely to manifest covid-19 related symptoms of fever and myalgia than non-pregnant women of reproductive age and are potentially more likely to need intensive care treatment for covid-19. Pre-existing comorbidities, high maternal age, and high body mass index seem to be risk factors for severe covid-19. Preterm birth rates are high in pregnant women with covid-19 than in pregnant women without the disease.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42020178076.

READERS' NOTE

This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication.

Introduction

Since the first report (December 2019) of the novel coronavirus disease 2019 (covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of confirmed cases and associated mortality and morbidity have increased rapidly.[1 2] Pregnant women are considered a high risk group because of concerns about the effect of covid-19 on them during and after pregnancy, and on their neonates.[3] Quantification of the rates of covid-19, its risk factors, clinical manifestations, and outcomes is key to planning clinical maternal care and management in an evolving pandemic scenario.[4]

Publications on covid-19 in pregnancy have risen steeply through individual case reports, case series, observational studies, and systematic reviews. As of 26 June 2020, more than 86 reviews have been published in this area,[5-10] with a further 94 registered in PROSPERO.[8 11] The early reviews mostly included case reports and case series that were often inappropriately meta-analysed, leading to biased estimates.[12] Subsequent reviews differed little from each other, often including similar primary studies, many with duplicate data. These reviews became quickly outdated as new evidence emerged. To date, no review has comprehensively evaluated the comparative data concerning pregnant and recently pregnant women and non-pregnant women with covid-19. Moreover, the sampling frames in primary studies have varied, ranging from universal SARS-CoV-2 testing for all pregnant women admitted to hospital[13 14] to symptom based testing.[15 16] Testing strategies have also differed within and between countries, with diagnosis in many early studies based on epidemiological risk assessment and clinical features without confirmed infection, which need to be considered in the analysis.[17] Limitations in the external and internal validity of studies make it challenging for guideline developers and policy makers to make evidence based recommendations for the management of pregnant and recently pregnant women with covid-19.

We began a living systematic review to determine the clinical manifestations of covid-19 in pregnant and recently pregnant women, identify the risk factors for complications, and quantify maternal and perinatal outcomes. This systematic review will be updated on a regular basis.

Methods

Our systematic review is based on a prospectively registered protocol (PROSPERO CRD42020178076; registered 22 April 2020)[18] to evaluate a series of research questions on covid-19 during and after pregnancy. We report our findings on the rates, clinical manifestations, risk factors, and maternal and perinatal outcomes in women with covid-19 in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations (see appendix 1). As more relevant data become available, we shall address the research questions in our published protocol. Each cycle of our living systematic review involves weekly search updates (rounds), with analysis performed every 2-4 weeks for our monthly reporting through a dedicated website, with early analysis if new definitive evidence emerges. We plan to regularly review the planned frequency of updates.

Literature search

We performed a systematic search of major databases: Medline, Embase, Cochrane database, WHO (World Health Organization) COVID-19 database, China National Knowledge Infrastructure (CNKI), and Wanfang databases from 1 December 2019 to 26 June 2020 for relevant studies on covid-19 in pregnant and recently pregnant women. To identify potential studies, we coordinated our search efforts with the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre), the WHO Library, and the Cochrane Gynaecology and Fertility group. Additional searches were conducted of preprint servers, blogs, websites that serve as repositories for covid-19 studies, social media, guidelines, and reference lists of included studies and unpublished data. We also searched the Living Overview of the Evidence (LOVE) platform from 11 to 26 June 2020.[19] We contacted established groups that were coordinating or conducting surveillance and studies in pregnant women with covid-19, such as the WHO Maternal, Newborn, Child and Adolescent health (MNCAH) covid-19 research network and the International Network of Obstetric Survey Systems (INOSS) for information on published and upcoming data. No language restrictions were applied. Appendix 2 provides details of the search strategies and databases searched.

Study selection

Two reviewers independently selected studies using a two stage process: they first screened the titles and abstracts of studies and then assessed the full text of the selected studies in detail for eligibility. A total of eight reviewers contributed to study selection.

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Disagreements were resolved through discussion with a third reviewer (ST or JA). We excluded studies if the duplicate data for all outcomes of interest were published elsewhere, as reported by the study authors, or when the characteristics of the mother or neonate matched the setting, characteristics, and duration of another study. When we suspected an overlap of data between studies, the study that provided comparative data was included. When there was uncertainty about duplicate data, we contacted the authors of primary studies.

We defined women as having confirmed covid-19 if they had laboratory confirmation of covid-19 infection irrespective of clinical signs and symptoms.[20] Women with a diagnosis based only on clinical or radiological findings were defined as having suspected covid-19. The recently pregnant group comprised women in the postpartum and post-abortion period. We included studies that compared covid-19 rates, clinical manifestations (symptoms, laboratory and radiological results), risk factors, and associated mortality and morbidity between pregnant and recently pregnant and non-pregnant women of reproductive age, and those that compared maternal and perinatal outcomes in pregnant women with and without covid-19. Studies on non-comparative cohorts with a minimum of 10 participants were included if they reported on the rates and clinical manifestations of covid-19 and relevant outcomes in pregnant and recently pregnant women. We defined cohort studies as those that sampled participants on the basis of exposure, followed-up participants over time, and ascertained the outcomes.[21] The PROSPERO protocol provides a full list of the risk factors, clinical features, and outcomes evaluated.[18]

The sampling frames for detecting covid-19 included universal screening and testing, when all women were assessed for covid-19 using reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 or chest computed tomography; risk based testing on the basis of epidemiological history and clinical manifestations by National Health Commission of China (NHCC) guidelines[17]; and symptom based when testing was performed on women with symptoms and those with a history of contact with affected individuals. We defined the population as being selected when only specific groups of women were included, such as those undergoing caesarean section or in the third trimester. We categorised studies as a high risk group if only women with any pre-existing medical or obstetric risk factors were included, low risk if women did not have any risk factors, and any risk if all women were included.

Study quality assessment and data extraction

The quality of the comparative cohort studies was assessed for selection, comparability, and outcome ascertainment bias using the Newcastle Ottawa scale.[22] Studies achieving four stars for selection, two for comparability, and three for ascertainment of the outcome were considered to have a low risk of bias. Studies achieving two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have a medium risk of bias, and any study achieving one star for selection or outcome ascertainment, or zero for any of the three domains, was regarded as having a high risk of bias. We assessed the quality of studies reporting on the prevalence of clinical manifestations or outcomes for internal and external validity using an existing tool.[23] The following were considered as low risk of bias for external validity: representative of national population for relevant variables (population), representative of target population (sampling frame), random selection (selection bias), and more than 75% response rate in individuals with and without the outcome (non-response bias).[23] Two independent reviewers extracted data using a pre-piloted form.

Statistical analysis

We pooled the comparative dichotomous data using random effects meta-analysis and summarised the findings as odds ratios with 95% confidence intervals. To combine comparative continuous data with dichotomous data we transformed standardised mean differences to logarithm odds ratios, assuming a normal underlying distribution.[24] We pooled the dichotomous non-comparative data for rates of clinical manifestations and maternal and perinatal outcomes as proportions with 95% confidence intervals using Dersimonian and Laird random effects meta-analysis after transforming data using Freeman-Tukey double arcsin transformation. Heterogeneity was reported as I^2 statistics. We undertook subgroup analysis by country status (high versus low and middle income), sampling frame (universal, risk based, and symptom based testing, including not reported), and risk status of women in the studies (high, low, any). Sensitivity analysis was performed by restricting the analysis to women with confirmed covid-19, study quality (high, low), and population (unselected, selected). All analyses were done with Stata (version 16).

Patient and public involvement

The study was supported by Katie's Team, a dedicated patients and public involvement group in Women's Health. The team was involved in the conduct, interpretation, and reporting of this living systematic review through participation in virtual meetings.

Results

After removing duplicates from 49 684 citations, 20 625 unique citations were identified and 77 cohort studies (55 comparative, 22 non-comparative) were included in the systematic review (fig 1).

Characteristics of included studies

Of the 77 studies, 26 (34%) were from the United States, 24 from China (31%), seven from Italy, six from Spain, three each from the United Kingdom and France, and one each from Belgium, Brazil, Denmark, Israel, Japan,

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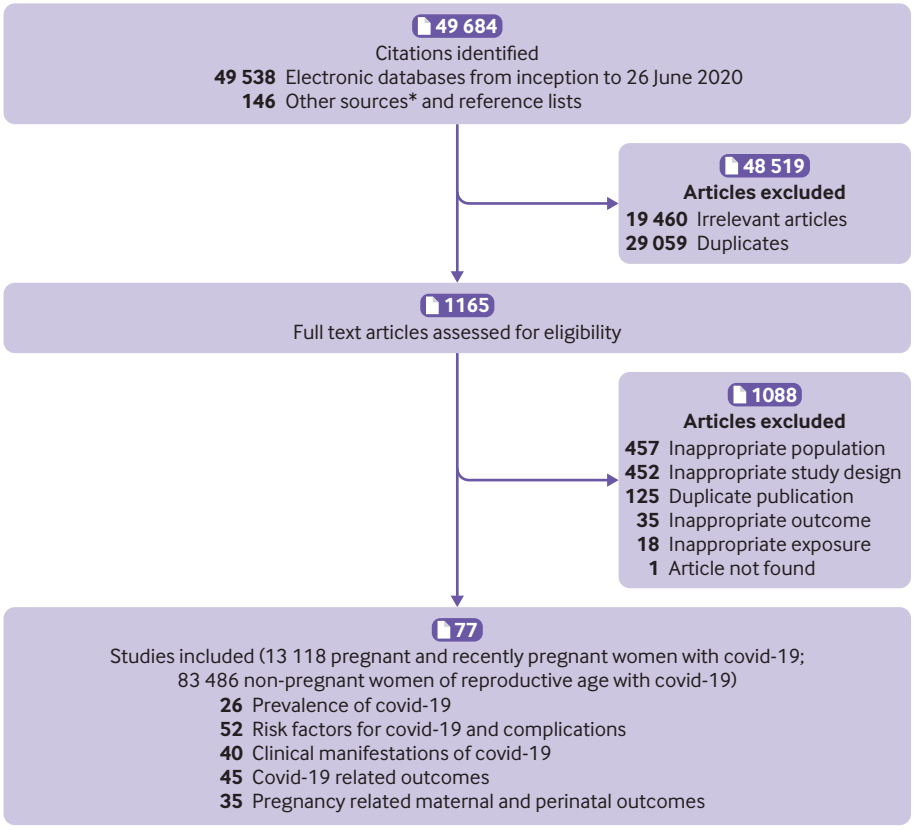

Fig 1 | Study selection process. *Twitter, national reports, blog by J Thornton, ObG Project, COVID-19 and Pregnancy Cases, www.obgproject.com/2020/04/07/covid-19-research-watch-with-dr-jim-thornton/ (accessed 12 May 2020); EPPI-Centre, COVID-19: a living systematic map of evidence, http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx (accessed 12 May 2020); Norwegian Institute of Public Health, NIPH systematic and living map on COVID-19 evidence, www.nornesk.no/forskningskart/NIPH_mainMap.html (accessed 19 May 2020); Johns Hopkins University Center for Humanitarian Health; COVID-19, Maternal and Child Health, Nutrition, http://hopkinshumanitarianhealth.org/empower/advocacy/covid-19/covid-19-children-and-nutrition/ (accessed 2 June 2020); ResearchGate, COVID-19 research community, www.researchgate.net/community/COVID-19 (accessed 2 June 2020); and Living Overview of the Evidence, Coronavirus disease (COVID-19), https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?population=5d062d5fc80dd41e58ba8459 (accessed 16 June 2020)

Mexico, the Netherlands, and Portugal. All the studies tested respiratory samples using RT-PCR to confirm the presence of SARS-CoV-2; 23 studies additionally diagnosed covid-19 based on clinical suspicion. Eight studies (95 247 women) compared pregnant populations with non-pregnant populations,[25-32] and four studies (2230 women) compared pregnant women with covid-19 versus pregnant women without covid-19.[33-36] Forty cohort studies reported on clinical manifestations (13 018 pregnant, 85 084 non-pregnant women),[25-32 35-66] 45 studies reported on covid-19 related maternal outcomes (14 094 pregnant, 85 169 non-pregnant women),[25-32 35-51 53-59 61-74] and 35 studies reported on pregnancy related maternal (6279 women) and perinatal outcomes (2557 neonates)[13 25 27 29 30 32-41 43-47 49-50 54 55 57 59 61 62 64-67 69 70 75] (see appendix 3). The sampling frames included universal testing (29 studies), risk based NHCC guidelines (22 studies), and symptom based (19 studies) strategies. Eleven studies did not report the sampling strategy.

Quality of included studies

Overall, 67% (37/55) of the comparative cohort studies evaluated using the Newcastle Ottawa scale had an overall low risk of bias (see appendix 4a). Forty nine (89%) had a low risk of bias for study selection and six (11%) had a medium risk. The risk of bias for comparability of cohorts was low in nine of the studies (16%), medium in 45 (82%), and high in one (2%). For outcome assessment of the cohorts, 12 (22%) studies had a low risk of bias, 42 (76%) a medium risk, and one (2%) a high risk. Quality assessment of the prevalence studies for external validity showed a low risk of bias for representativeness in 13% (10/76) of the studies, sampling in 26% (20/76), selection in 74% (56/76), and non-response in 96% (73/76). For internal validity, there was low risk of bias for data collection in 95% (72/76) of the studies, case definition in 36% (27/76), measurement in 99% (75/76), differential verification in 86% (65/76), adequate follow-up in 22% (17/76), and appropriate numerator and denominator in 83% (63/76) (see appendix 4b).

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Rates of covid-19 in pregnant and recently pregnant women

The overall rate of covid-19 diagnosis in pregnant and recently pregnant women attending or admitted to hospital for any reason was 10% (95% confidence interval 7% to 14%; 26 studies, 11 432 women; fig 2). Rates varied by sampling strategy: of the women sampled by universal screening, 7% (4% to 10%; 18 studies, 6247 women) were diagnosed as having covid-19 compared with 18% (10% to 28%; 8 studies, 4928 women) of women sampled on the basis of symptoms. All studies with a prevalence rate for covid-19 greater than 15% were from the US, except for one study, which was from France.[76] One in 20 asymptomatic mothers (5%, 2% to 9%; 11 studies) attending or admitted to hospital had a diagnosis of covid-19 (see appendix 5a). Three quarters (74%, 51% to 93%; 11 studies) of the 162 pregnant women with covid-19 in the universal screening population were asymptomatic (see appendix 5b). Based on data from a small number of studies, a diagnosis of covid-19 in pregnancy was associated with maternal obesity (odds ratio 1.75, 95% confidence interval 1.34 to 2.30; 1 study, 1080 women), pre-existing comorbidities (1.64, 1.25 to 2.13; 1 study, 1121 women), asthma (1.71, 1.03 to 2.84; 2 studies, 1250 women), history of covid-19 in the support person (44.56, 14.90 to 133.28; 1 study, 199 women), and gestational diabetes (2.42, 1.55 to 3.79; 1 study, 1121 women) (see appendix 6a).

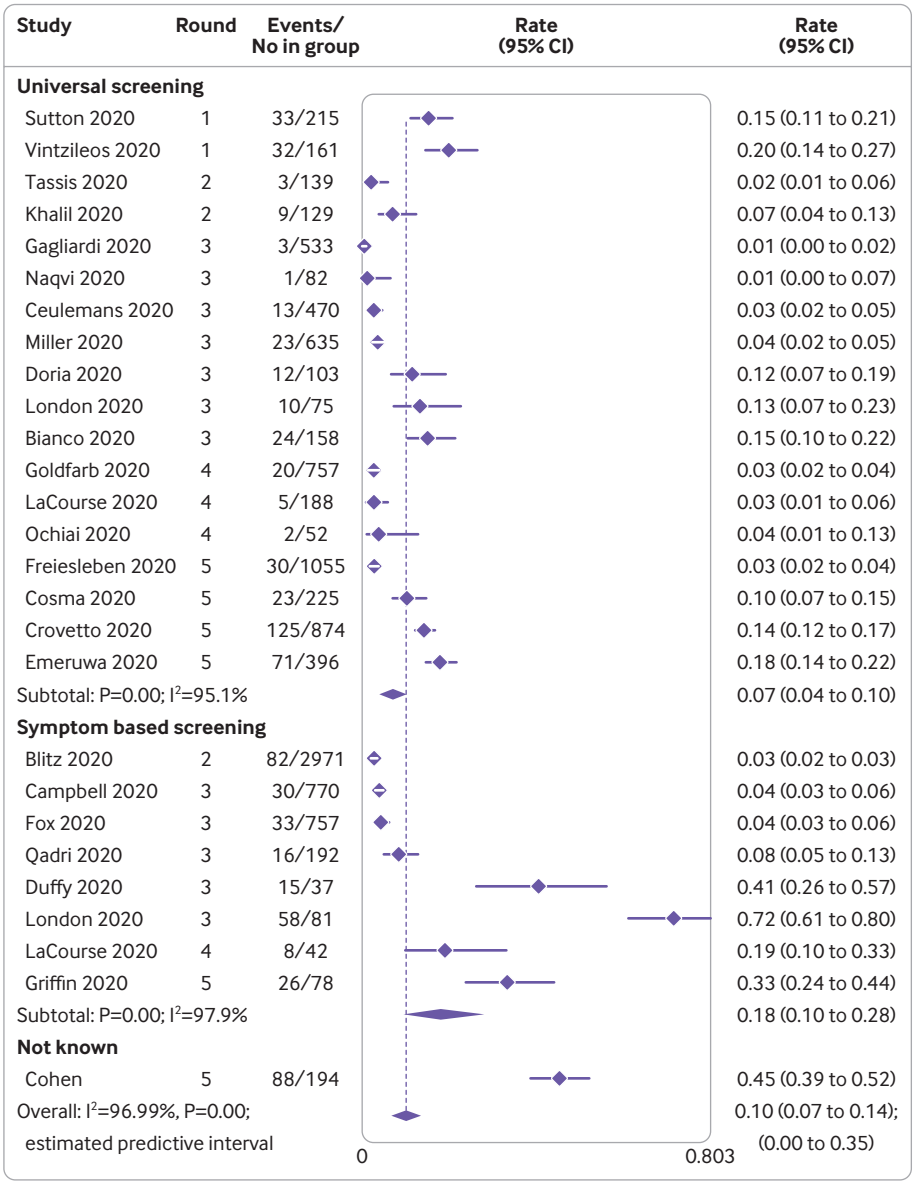

Fig 2 | Prevalence of severe acute respiratory syndrome coronavirus 2 in pregnant and recently pregnant women identified by various sampling strategies. Meta-analysis includes one study (Liao 2020) screened using National Health Commission China criteria with no events. Symptom based screening includes screening based on symptoms or history of contact with individuals with covid-19. Round number represents search strategy updates in the living systematic review

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Clinical manifestations of covid-19 during pregnancy and after delivery

The most common symptoms reported by pregnant and recently pregnant women with suspected or confirmed covid-19 were fever (40%) and cough (39%); lymphopaenia (35%) and raised C reactive protein levels (49%) were the most common laboratory findings (fig 3). Compared with non-pregnant women of reproductive age with covid-19, pregnant and recently pregnant women with the disease were less likely to manifest symptoms of fever (0.43, 0.22 to 0.85; 5 studies, 80 521 women) and myalgia (0.48, 0.45 to 0.51; 3 studies, 80 409 women) (fig 4). A history of pre-existing diabetes was more often observed in pregnant women with covid-19 than in non-pregnant women with the disease (1.78, 1.03 to 3.05; 3 studies, 91 595 women) (see appendix 6b). Sensitivity analysis restricted to various sampling frames showed lower estimates of fever, cough, and dyspnoea in the universal screening population and higher estimates in the symptom based population (see appendix 7). The rates of clinical manifestations were similar to the overall estimates when the analysis was restricted to only women with RT-PCR confirmed covid-19, unselected populations, and women with any risk (see appendix 7).

Outcomes related to covid-19 in pregnant and recently pregnant women

Overall, 73 pregnant women (26 studies, 11 580 women) with confirmed covid-19 died from any cause (0.1%, 95% confidence interval 0.0% to 0.7%). Severe covid-19 was diagnosed in 13% (6% to 21%; 21 studies, 2271 women) of pregnant and recently pregnant women with suspected or confirmed covid-19; 4% (2% to 7%; 17 studies, 10 901 women) of the pregnant women with covid-19 were admitted to an intensive care unit, 3% (1% to 5%; 13 studies, 10 713 women) required invasive ventilation, and 0.4% (0.1% to 0.9%; 9 studies, 1935 women) required extracorporeal membrane oxygenation (fig 3). Appendix 8 provides the rates of complications by sampling strategy. Compared with non-pregnant women of reproductive age with covid-19, the odds of admission to the intensive care unit (1.62, 95% confidence interval 1.33 to 1.96) and need for invasive ventilation (1.88, 1.36 to 2.60) were higher in pregnant and recently pregnant women (four studies, 91 606 women) (table 1). Maternal risk factors associated with severe covid-19 were increasing age (1.78, 1.25 to 2.55; 4 studies, 1058 women), high body mass index (2.38, 1.67 to 3.39; 3 studies, 877 women), chronic hypertension (2.0, 1.14 to 3.48; 2 studies, 858 women), and pre-existing diabetes (2.51, 1.31 to 4.80; 2 studies, 858 women) (fig 5). Pre-existing maternal comorbidity was associated with admission to an intensive care unit (4.21, 1.06 to 16.72; 2 studies, 320 women) and the need for invasive ventilation (4.48, 1.40 to 14.37; 2 studies, 313 women) (table 2).

Maternal and perinatal outcomes in pregnant and recently pregnant women with covid-19

In pregnant and recently pregnant women with covid-19 the rate of overall preterm birth was 17% (95% confidence interval 13% to 21%; 30 studies, 1872 women) and of spontaneous preterm birth was 6% (3% to 9%; 10 studies, 870 women) (fig 3). In pregnant and recently pregnant women with covid-19 compared with pregnant and recently pregnant women without the disease, the odds of any preterm birth (3.0, 95% confidence interval 1.15 to 7.85; 2 studies, 339 women) were higher, but no differences were observed in other maternal outcomes (table 1). Eighteen stillbirths (27 studies; 2837 offspring) and six neonatal deaths (26 studies; 1728 neonates) occurred among pregnant and recently pregnant women with covid-19, resulting in negligible risks (fig 3). Overall, 25% (95% confidence interval 14% to 37%; 17 studies, 1348 women) of neonates born to women with covid-19 were admitted to the neonatal unit (fig 3), with a higher risk of admission (odds ratio 3.13, 95% confidence interval 2.05 to 4.78; 1 study, 1121 neonates) than those born to mothers without the disease in one study with historical controls. No differences were observed for other perinatal outcomes. Appendix 9 provides the rates of covid-19 related and pregnancy related outcomes for the individual studies.

Discussion

In this living systematic review, we found that one in 10 pregnant or recently pregnant women who are attending or admitted to hospital for any reason are diagnosed as having suspected or confirmed covid-19, although the rates vary by sampling strategy. The covid-19 related symptoms of fever and myalgia manifest less often in pregnant and recently pregnant women than in non-pregnant women of reproductive age. Whereas testing for SARS-CoV-2 in non-pregnant women is based on symptoms or contact history, testing in pregnant women is usually done when they are in hospital for reasons that might not be related to covid-19. Pregnant or recently pregnant women with covid-19 seem to be at increased risk of requiring admission to an intensive care unit or invasive ventilation. Increased maternal age, high body mass index, and pre-existing comorbidities might be associated with severe disease. Pregnant women with covid-19 are at increased risk of delivering preterm and their babies being admitted to the neonatal unit. But overall rates of spontaneous preterm births are not high. Stillbirth and neonatal death rates are low in women with suspected or confirmed covid-19. All comparative findings are based on small numbers of studies, despite the large sample sizes. Substantial heterogeneity was observed in the estimates for rates of clinical manifestations and outcomes, which varied by sampling frames, participant selection, and risk status of the participants.

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Study	Studies	Events/ No in group	Proportion (95% CI)	Proportion (95% CI)	I^2 (%) (P value)	Range
Clinical manifestations						
Symptoms						
Fever	29	2733/8328		0.40 (0.31 to 0.49)	97.4 (0.00)	(0.11-0.73)
Cough	28	3432/8317		0.39 (0.31 to 0.47)	96.8 (0.00)	(0.03-0.81)
Dyspnoea	22	1928/8159		0.19 (0.13 to 0.26)	96.2 (0.00)	(0.00-0.62)
Myalgia	9	1411/6078		0.10 (0.05 to 0.17)	90.7 (0.00)	(0.00-0.25)
Ageusia	3	24/310		0.15 (0.00 to 0.41)	93.6 (0.00)	(0.03-0.28)
Diarrhoea	17	659/7525		0.07 (0.05 to 0.09)	65.5 (0.00)	(0.00-0.18)
Laboratory findings						
Raised white cell count	6	50/251		0.27 (0.09 to 0.51)	92.3 (0.00)	(0.03-0.52)
Lymphopaenia	15	262/780		0.35 (0.26 to 0.45)	85.6 (0.00)	(0.09-0.90)
Thrombocytopaenia	7	36/428		0.08 (0.02 to 0.18)	85.3 (0.00)	(0.01-0.35)
Abnormal liver function test results	9	51/491		0.11 (0.05 to 0.18)	74.1 (0.00)	(0.00-0.29)
Raised procalcitonin level	5	60/261		0.21 (0.00 to 0.59)	96.6 (0.00)	(0.00-0.97)
Raised C reactive protein level	7	174/426		0.49 (0.36 to 0.63)	86.2 (0.00)	(0.23-0.71)
Radiological findings						
Ground glass appearance	10	246/387		0.69 (0.41 to 0.91)	96.5 (0.00)	(0.09-1.00)
Any abnormality on computed tomography	20	599/1968		0.65 (0.46 to 0.82)	98.4 (0.00)	(0.02-1.00)
Maternal and perinatal outcomes						
Covid related outcomes						
All cause mortality	26	73/11 580		0.00 (0.00 to 0.01)	80.2 (0.00)	(0.00-0.07)
Admission to intensive care unit	17	323/10 901		0.04 (0.02 to 0.07)	93.6 (0.00)	(0.00-0.13)
Severe covid-19	21	417/2271		0.13 (0.06 to 0.21)	95.5 (0.00)	(0.00-1.00)
Invasive ventilation	13	155/10 713		0.03 (0.01 to 0.05)	93.5 (0.00)	(0.00-0.09)
ECMO	9	16/1935		0.00 (0.00 to 0.01)	0.0 (0.93)	(0.00-0.01)
Oxygen, cannula	13	243/1281		0.30 (0.14 to 0.48)	97.1 (0.00)	(0.02-1.00)
ARDS	6	270/1006		0.09 (0.00 to 0.33)	98.7 (0.00)	(0.00-0.51)
Pneumonia	23	729/2577		0.49 (0.35 to 0.63)	97.9 (0.00)	(0.00-1.00)
Cardiac, liver, renal failure	7	7/737		0.00 (0.00 to 0.01)	10.6 (0.35)	(0.00-0.13)
Pregnancy related outcomes						
Preterm birth <37 weeks	30	386/1872		0.17 (0.13 to 0.21)	71.5 (0.00)	(0.00-0.59)
Spontaneous preterm birth	10	56/870		0.06 (0.03 to 0.09)	55.0 (0.02)	(0.02-0.31)
PPROM <37 weeks	8	28/436		0.05 (0.03 to 0.08)	0.0 (0.66)	(0.03-0.17)
Caesarean section	28	1060/1933		0.65 (0.57 to 0.73)	91.3 (0.00)	(0.33-1.00)
Vaginal delivery	27	856/1916		0.35 (0.27 to 0.43)	91.4 (0.00)	(0.00-0.67)
Postpartum haemorrhage	5	13/250		0.03 (0.00 to 0.08)	45.6 (0.14)	(0.01-0.09)
Offspring outcomes						
Stillbirth	27	18/2837		0.00 (0.00 to 0.00)	0.0 (1.00)	(0.00-0.02)
Neonatal death	26	6/1728		0.00 (0.00 to 0.00)	0.0 (1.00)	(0.00-0.01)
Admission to neonatal unit	17	368/1348		0.25 (0.14 to 0.37)	94.9 (0.00)	(0.00-1.00)
Neonatal sepsis	2	2/51		0.04 (0.00 to 0.12)	Not estimable	(0.03-0.06)
Abnormal Apgar score	14	11/500		0.01 (0.00 to 0.02)	0.0 (0.64)	(0.00-0.06)
Fetal distress	7	25/293		0.08 (0.05 to 0.12)	0.0 (0.74)	(0.04-0.15)

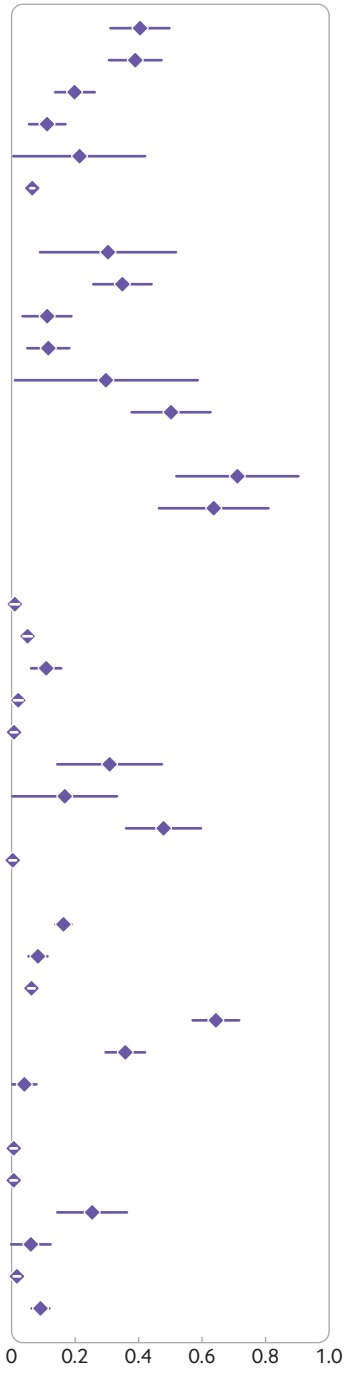

Fig 3 | Rates of clinical manifestations of coronavirus disease (covid-19) in pregnant women and recently pregnant women with suspected or confirmed covid-19 and associated maternal and perinatal outcomes. ECMO=extracorporeal membrane oxygenation; ARDS=acute respiratory distress syndrome; PPROM=preterm premature rupture of membranes

Strengths and limitations of this review

In this unprecedented pandemic situation, where evidence is rapidly produced and published in various formats, our living systematic review underpinned by robust methods and continually updated at regular intervals is relevant for several reasons. Firstly, it addresses important research questions relevant to clinical decision making and policies. Secondly, uncertainties remain for key outcomes that require further evidence. Thirdly, the rapid turnover of evidence in various formats requires assessments of study quality and regular updating of the findings.

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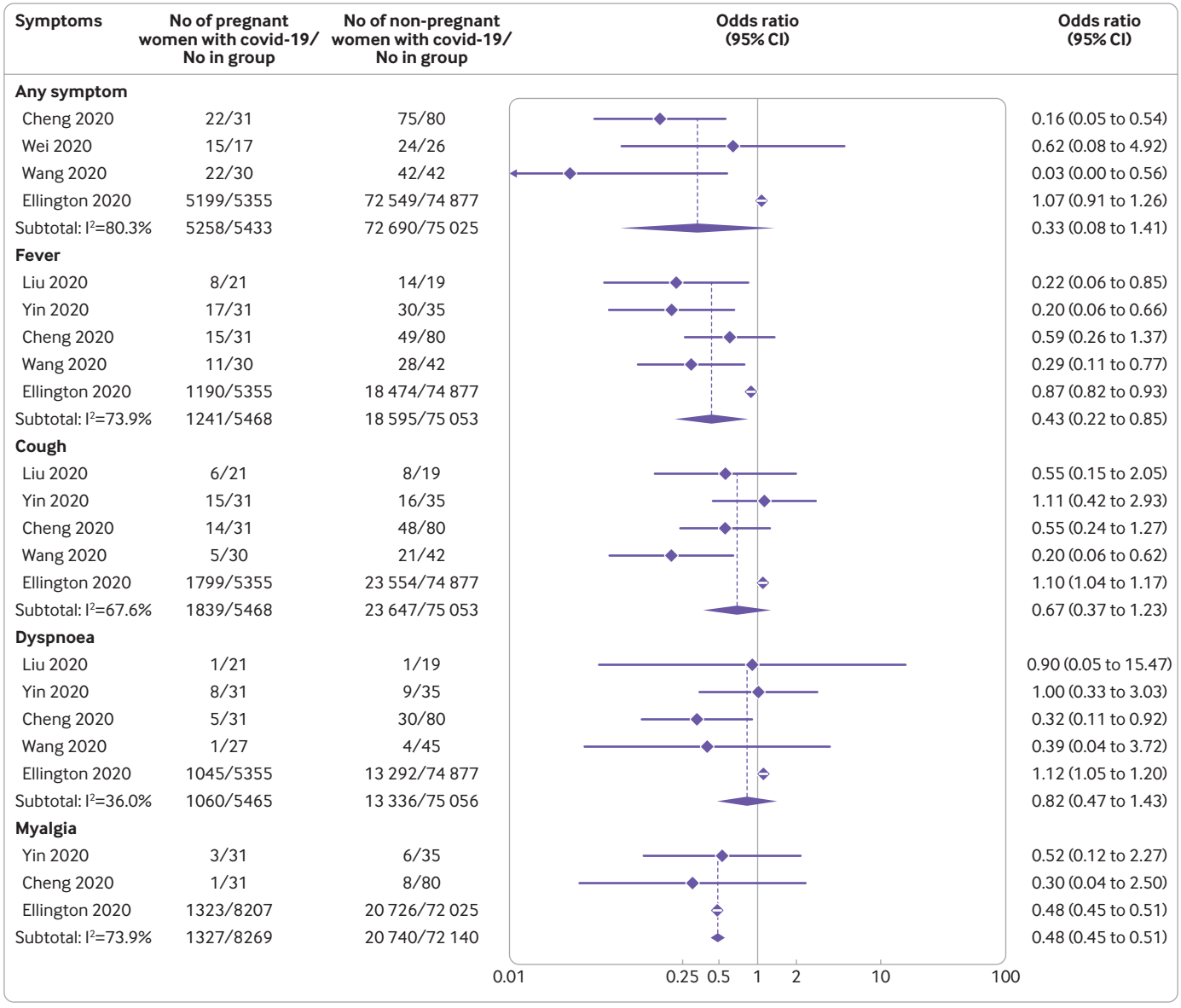

Note: Weights are from random effects analysis

Fig 4 | Clinical manifestations of coronavirus disease (covid-19) in pregnant and recently pregnant women compared with non-pregnant women of reproductive age with covid-19

Finally, our living systematic review will produce a strong evidence base for living guidelines on covid-19 and pregnancy.

We undertook a comprehensive search and coordinated our efforts with key organisations and research groups, such as WHO, the Cochrane Centre, and EPPI-Centre. To minimise risk of bias we restricted our meta-analysis to cohort studies, and we reported the quality of the included studies. By contacting the authors and obtaining reports not published in PubMed, we minimised the risk of missing relevant studies. Our systematic review has a large sample size and it is continuously increasing. Our living meta-analyses framework will enable us to rapidly update the findings as new data emerge. We undertook extensive work to ensure that duplicate data are not included. Our various comparative analyses allowed us to comprehensively assess the association between pregnancy and covid-19 related outcomes, covid-19 and pregnancy outcomes, risk factors for SARS-CoV-2 infection, and complications. Our review helps to understand the variations in estimates through sensitivity analyses by sampling strategies, population characteristics, and risk factors, and it provides confidence in the rates of reported outcomes.

Our systematic review also has limitations. The primary studies used varied sampling frames to identify women with covid-19, comprised women with suspected and confirmed covid-19, and primarily reported on pregnant women who required visits to hospital, including for childbirth, thereby affecting the generalisability of the estimates. Although our

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Table 1 | Outcomes in pregnant and recently pregnant women with coronavirus disease 2019 (covid-19)

Outcomes	No of studies	Women (No with event/No in group (%))		Odds ratio (95% CI)	I^2 (%)
		Pregnant women with covid-19	Comparison group		
Comparison group: non-pregnant women of reproductive age with covid-19					
All cause mortality	4	16/8282 (0.2)	208/83 327 (0.2)	0.81 (0.49 to 1.33)	0
ICU admission	4	121/8276 (1.5)	758/83 330 (0.9)	1.62 (1.33 to 1.96)	0
Invasive ventilation	4	43/8276 (0.5)	226/83 330 (0.3)	1.88 (1.36 to 2.60)	0
ECMO	1	0/31 (0)	0/80 (0)	2.56 (0.05 to 131.60)	NE
Oxygen through nasal cannula	2	8/48 (16.7)	49/106 (46.2)	0.21 (0.04 to 1.13)	65.7
ARDS	1	0/17 (0)	0/26 (0)	1.51 (0.03 to 79.93)	NE
Major organ failure	1	0/17 (0)	0/26 (0)	1.51 (0.03 to 79.93)	NE
Comparison group: pregnant women without covid-19					
Maternal outcomes:					
All cause mortality	1*	5/427 (1.2)	0/694 (0)	18.08 (1.00 to 327.83)	NE
ICU admission	1*	40/427 (9.4)	1/694 (0.1)	71.63 (9.81 to 523.06)	NE
Preterm birth <37 weeks	2	7/44 (15.9)	18/295 (6.1)	3.01 (1.16 to 7.85)	0.9
Caesarean section	3*	184/491 (37.5)	577/1676 (34.4)	2.02 (0.67 to 6.10)	87.5
Perinatal outcomes:					
Stillbirth	1*	3/427 (0.7)	2/694 (0.3)	2.45 (0.41 to 14.71)	NE
Neonatal death	1*	2/427 (0.5)	1/694 (0.1)	3.26 (0.30 to 36.07)	NE
Admission to neonatal unit	1*	64/427 (15.0)	37/694 (5.3)	3.13 (2.05 to 4.79)	NE
Abnormal Apgar score at 5 minutes	1	0/30 (0)	12/740 (1.6)	0.96 (0.06 to 16.51)	NE
Fetal distress	1	3/34 (8.8)	12/242 (5.0)	1.86 (0.50 to 6.94)	NE

ICU=intensive care unit; ECMO=extracorporeal membrane oxygenation; ARDS=acute respiratory distress syndrome; NE=not estimable.
The denominator is number of pregnancies for all outcomes.
*Historical comparative cohort in UK Obstetric Surveillance System study.

sensitivity analyses aimed to tackle some of these problems, the numbers and sample sizes of the individual studies were too small to identify differences between the subgroups. The timing of assessment of the clinical manifestations of disease was generally not available. The definitions of symptoms, tests, and outcomes were heterogeneous. Furthermore, poor reporting of the criteria for caesarean section, admissions to the neonatal unit, and the causes of preterm birth, made it difficult to disentangle iatrogenic effect from the true impact of the disease. There is a paucity of comparative data to assess the risk of severe disease in pregnant women compared with non-pregnant women in similarly aged groups, and to compare pregnancy outcomes in women with and without covid-19. Not many studies reported outcomes by trimester for symptom onset, making it difficult to assess the rates of miscarriage and postpartum complications. For some outcomes, the findings were influenced by a single large study.[26] Many studies had to be excluded as we could not rule out potential overlap in the study populations.

Comparison with existing evidence

Alongside the spread of the pandemic, a shift has occurred in the types of studies published, with initial studies involving pregnant women from epidemic regions in China, followed by reports of large regional and national datasets from the US, UK, Netherlands, Spain, and, more recently, Latin American countries. The study design has also changed from initial small case series and case reports to large observational data, with recent studies also providing comparative data. The prevalence of covid-19 varied widely between studies, particularly when sampling was done based on symptoms or history of contact, highlighting the variations in criteria for testing. Moreover, the findings only relate to those women attending hospital for any reason. The true prevalence of covid-19 in pregnancy is likely to be lower when all pregnant women are included.

In the recent cohort study of all individuals admitted with covid-19 in the UK, the cluster of respiratory symptoms of cough, fever, and breathlessness were observed in more than two thirds of individuals,[77] similar to reported rates in the US and China.[78-80] But in our review, fewer pregnant and recently pregnant women with covid-19 manifested these symptoms than the non-pregnant population, indicating possible high rates of asymptomatic presentation in this population. This is likely because of the strategy of universal screening for covid-19 in pregnancy and the low thresholds for testing than in non-pregnancy. Despite the possibility of the above strategies detecting pregnant women with mild disease, we observed an increase in admissions to the intensive care unit and need for invasive ventilation compared with non-pregnant women of reproductive age with covid-19. The findings were mainly influenced by the recent large Centers for Disease Control and Prevention report from the US.[26] Pregnancy status was not ascertained in a large proportion of women of reproductive age in the CDC report that could affect the estimates. Furthermore, the outcomes for which the data were missing were considered to be absent in the report, thereby incurring bias. The pooled estimates for severe covid-19 and admission to an intensive care unit were, however, still relatively high in the non-comparative data, indicative of a potential high risk in pregnancy. This is supported by the recent analysis in a Swedish study suggesting a high risk of admission to an intensive care unit and invasive ventilation in pregnant women than non-pregnant women.[81]

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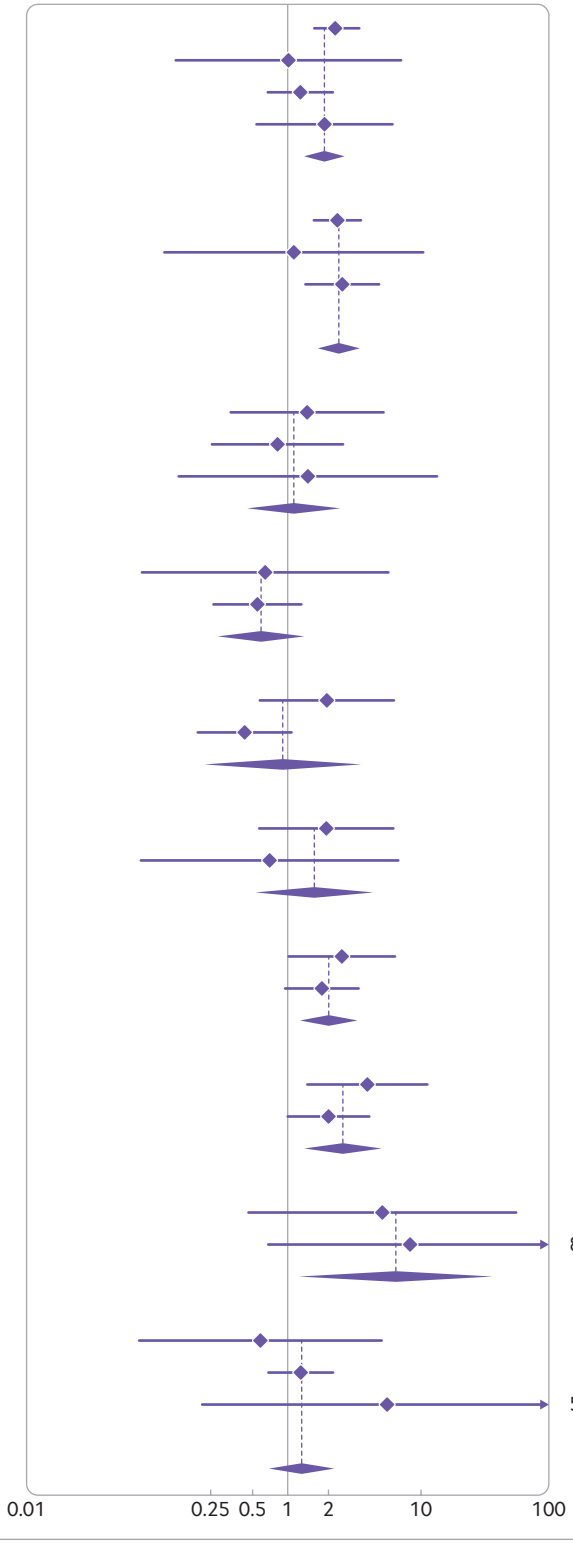
Risk factors	No of pregnant women with risk factor and severe covid-19/No in group	No of pregnant women with risk factor without severe covid-19/No in group	Odds ratio (95% CI)	Odds ratio (95% CI)
Age*				
Kayem 2020	59/128	135/489		2.24 (1.50 to 3.35)
Martinez-Perez 2020	2/4	39/78		1.00 (0.13 to 7.46)
Khoury 2020	22/75	43/166		1.19 (0.65 to 2.18)
Chen 2020 (continuous age)	n/9	n/109		1.87 (0.55 to 6.42)
Subtotal: I^2=9%	83/216	219/842		1.78 (1.25 to 2.55)
Body mass index				
Kayem 2020	46/128	93/489		2.39 (1.56 to 3.66)
Martinez-Perez 2020	1/4	18/78		1.11 (0.11 to 11.35)
Khoury 2020	43/62	55/116		2.51 (1.31 to 4.81)
Wu 2020	0/0	0/13		Excluded
Subtotal: I^2=0%	90/194	166/696		2.38 (1.67 to 3.39)
Multiparity				
Chen 2020	5/9	46/97		1.39 (0.35 to 5.47)
Savasi 2020	8/14	39/63		0.82 (0.25 to 2.66)
Martinez-Perez 2020	3/4	53/78		1.42 (0.14 to 14.29)
Subtotal: I^2=0%	16/27	138/238		1.07 (0.46 to 2.46)
Third trimester				
Yan 2020	7/8	99/108		0.64 (0.07 to 5.76)
Andrikopoulou 2020	22/34	94/124		0.59 (0.26 to 1.32)
Subtotal: I^2=0%	29/42	193/232		0.59 (0.28 to 1.27)
Non-white				
Savasi 2020	6/14	18/63		1.88 (0.57 to 6.17)
Khoury 2020	54/65	143/156		0.45 (0.19 to 1.06)
Subtotal: I^2=73%	60/79	161/219		0.86 (0.21 to 3.50)
Any comorbidity				
Savasi 2020	6/14	18/63		1.88 (0.57 to 6.17)
Martinez-Perez 2020	1/4	25/78		0.71 (0.07 to 7.14)
Subtotal: I^2=0%	7/18	43/141		1.53 (0.53 to 4.41)
Chronic hypertension				
Kayem 2020	7/128	11/489		2.51 (0.95 to 6.62)
Khoury 2020	18/75	25/166		1.78 (0.90 to 3.51)
Subtotal: I^2=0%	25/203	36/655		2.00 (1.14 to 3.48)
Pre-existing diabetes				
Kayem 2020	7/128	7/489		3.98 (1.37 to 11.57)
Khoury 2020	16/75	20/166		1.98 (0.96 to 4.08)
Subtotal: I^2=12%	23/203	27/655		2.51 (1.31 to 4.80)
Pre-eclampsia				
Yan 2020	1/8	3/108		5.00 (0.46 to 54.51)
Martinez-Perez 2020	1/4	3/78		8.33 (0.66 to 105.71)
Subtotal: I^2=0%	2/12	6/186		6.35 (1.11 to 36.22)
Gestational diabetes				
Andrikopoulou 2020	1/34	6/124		0.60 (0.07 to 5.13)
Kayem 2020	17/128	54/489		1.23 (0.69 to 2.21)
Martinez-Perez 2020	0/4	1/78		5.74 (0.20 to 161.79)
Yan 2020	0/0	9/116		Excluded
Subtotal: I^2=0%	18/166	70/807		1.23 (0.70 to 2.14)



Note: Weights are from random effects analysis

Fig 5 | Risk factors associated with severe coronavirus disease 2019 (covid-19) in pregnant and recently pregnant women. Symptom based screening: Savasi V, Kayem G; NHCC (National Health Commission China). Criteria based screening: Chen, Wu, Yan. All other studies used universal screening. Cut-off for age is 35 years or more, and for body mass index is 30 or more. *Includes one study with continuous measurement of risk factor

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Table 2 | Maternal characteristics associated with severe coronavirus disease 2019 (covid-19) and all cause death in pregnant and recently pregnant women with a diagnosis of covid-19

Maternal risk factors and outcomes	No of studies	Total No of women	Pregnant women (No with risk factor/No in group (%))		Odds ratio (95% CI)	I^2 (%)
			With outcome	Without outcome		
Age ≥35 years:						
Severe disease	4	1058	216*	842*	1.78 (1.25 to 2.55)	9
ICU admission	2	260	8/87 (9.2)	8/173 (4.6)	2.44 (0.43 to 14.01)	63
Invasive ventilation	1	178	3/65 (4.6)	2/113 (1.8)	2.69 (0.44 to 16.51)	NE
Maternal death	1	288	20/154 (13.0)	16/134 (11.9)	1.10 (0.55 to 2.22)	NE
Multiparity:						
Severe disease	3	265	16/154 (10.4)	11/111 (9.9)	1.07 (0.46 to 2.46)	0
ICU admission	1	42	4/22 (18.2)	4/20 (20.0)	0.89 (0.19 to 4.15)	NE
Body mass index ≥30:						
Severe disease	3	877	90/256 (35.2)	104/621 (16.7)	2.38 (1.67 to 3.39)	0
ICU admission	1	142	3/22 (13.6)	4/120 (3.3)	4.58 (0.95 to 22.09)	NE
Invasive ventilation	1	135	5/21 (23.8)	6/114 (5.3)	5.63 (1.54 to 20.59)	NE
Maternal death	2	596	6/62 (9.7)	37/534 (6.9)	2.57 (0.97 to 6.82)	0
Non-white ethnicity:						
Severe disease	2	298	60/221 (27.1)	19/77 (24.7)	0.86 (0.21 to 3.50)	73
ICU admission	1	42	5/20 (25.0)	3/22 (13.6)	2.11 (0.43 to 10.28)	NE
Maternal death	2	596	31/220 (14.1)	12/376 (3.2)	2.40 (0.94 to 6.11)	0
Any comorbidity:						
Severe disease	2	159	7/50 (14.0)	11/109 (10.1)	1.53 (0.53 to 4.41)	0
ICU admission	2	320	4/37 (10.8)	11/283 (3.9)	4.21 (1.06 to 16.72)	0
Invasive ventilation	2	313	6/36 (16.7)	10/277 (3.6)	4.48 (1.40 to 14.37)	0
Chronic hypertension:						
Severe disease	2	858	25/61 (41.0)	178/797 (22.3)	2.0 (1.14 to 3.48)	0
ICU admission	1	141	2/5 (40.0)	5/136 (3.7)	17.47 (2.37 to 129.02)	NE
Invasive ventilation	1	134	4/5 (80.0)	7/129 (5.4)	69.71 (6.85 to 709.34)	NE
Maternal death	2	596	5/29 (17.2)	38/567 (6.7)	3.38 (1.17 to 9.75)	0
Pre-existing diabetes:						
Severe disease	2	858	23/50 (46.0)	180/808 (22.3)	2.51 (1.31 to 4.80)	12
ICU admission	2	181	1/7 (14.3)	14/174 (8.0)	2.88 (0.44 to 18.96)	0
Invasive ventilation	1	132	1/6 (16.7)	9/126 (7.1)	2.60 (0.27 to 24.71)	NE
Maternal death	2	596	10/52 (19.2)	33/544 (6.1)	6.63 (0.27 to 161.45)	91
Asthma:						
Severe disease	3	857	17/61 (27.9)	149/796 (18.7)	1.86 (0.88 to 3.93)	22
Maternal death	2	596	3/22 (13.6)	40/574 (7.0)	2.04 (0.61 to 6.85)	0
Smoking:						
Severe disease	3	776	5/23 (21.7)	141/753 (18.7)	1.67 (0.64 to 4.40)	0
ICU admission	1	42	1/2 (50.0)	7/40 (17.5)	4.71 (0.26 to 84.77)	NE
Maternal death	1	308	0/10 (0)	7/298 (2.3)	1.85 (0.10 to 34.60)	NE
Gestation ≥28 weeks:						
Severe disease	2	274	29/222 (13.1)	13/52 (25.0)	0.59 (0.28 to 1.27)	0
Maternal death	1	273	22/190 (11.6)	12/83 (14.5)	0.78 (0.36 to 1.65)	NE
Gestational diabetes:						
Severe disease	4	973	18/88 (20.5)	148/885 (16.7)	1.23 (0.70 to 2.14)	0
Pre-eclampsia:						
Severe disease	2	198	2/8 (25.0)	10/190 (5.3)	6.36 (1.12 to 36.22)	0
ICU admission	1	42	6/6 (100.0)	2/36 (5.6)	179.40 (7.69 to 4186.05)	NE

ICU=intensive care unit; NE=not estimable.
*Includes one or more studies with continuous measurement of risk factor.

Similar to the general population, high body mass index and pre-existing comorbidity seemed to be risk factors for severity of covid-19 in pregnancy, including admission to an intensive care unit and invasive ventilation.[77] Complications related to covid-19 did not seem to be increased in women presenting in the third trimester or in multiparous women—but existing sample sizes are not large. Both chronic hypertension and pre-existing diabetes were associated with maternal death in pregnant women with covid-19, which are known risk factors in the general population. But it is not known if covid-19 was the direct cause of death for these women, and the numbers of studies are small. We observed an increase in rates of preterm birth in pregnant women with covid-19 compared with those without the disease. These preterm births could be medically indicated, as the overall rates of spontaneous preterm births in pregnant women with covid-19 was broadly similar to those observed in the pre-pandemic period. Although more than 60% of pregnant women underwent caesarean section in the non-comparative studies, we did not find a statistically significant difference in comparative studies of pregnant women with and without covid-19. The precision of the estimates is expected to improve with the publication of more data in the future. The overall

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rates of stillbirths and neonatal deaths do not seem to be higher than the background rates. The indications for admissions to the neonatal unit, observed in about a quarter of neonates delivered to mothers with covid-19, have not been reported. Local policies on observation and quarantine of infants with exposure to SARS-CoV-2 might have influenced these rates.

Relevance for clinical practice and research

Based on existing data, healthcare professionals should be aware that pregnant and recently pregnant women with covid-19 might manifest fewer symptoms than the general population, with the overall pattern similar to that of the general population. Emerging comparative data indicate the potential for an increase in the rates of admission to intensive care units and invasive ventilation in pregnant women compared with non-pregnant women. Mothers with pre-existing comorbidities will need to be considered as a high risk group for covid-19, along with those who are obese and of greater maternal age. Clinicians will need to balance the need for regular multidisciplinary antenatal care to manage women with pre-existing comorbidities against unnecessary exposure to the virus, through virtual clinic appointments when possible. Pregnant women with covid-19 before term gestation might need to be managed in a unit with facilities to care for preterm neonates.

Further data are needed to assess robustly if pregnancy related maternal and neonatal complications are increased in women with covid-19 than those without the disease. Similarly, the association between other risk factors such as ethnicity and pregnancy specific risk factors such as pre-eclampsia and gestational diabetes on both covid-19 related and pregnancy related outcomes needs evaluation. Pre-eclampsia was reported to be associated with severe covid-19 in small studies, but it requires further assessment as the clinical presentation of severe pre-eclampsia could mimic worsening covid-19.[82] Robust collection of maternal data by trimester of exposure, including the periconception period, is required to determine the effects of covid-19 on early pregnancy outcomes, fetal growth, and risk of stillbirth.

Systematic reviews are considered to be the highest quality evidence informing guidelines, and poor quality reviews will have a direct impact on clinical care. Despite the urgent need for evidence on the impact of covid-19 in pregnant women, systematic reviews and meta-analyses still need to adhere to the reporting guidelines on search criteria, quality assessment, and analysis. This is particularly important as large numbers of non-peer reviewed scientific papers and reports are currently available in the public domain in multiple versions. Primary studies need to explicitly state if duplicate data have been included to avoid double counting of participants in evidence synthesis. Individual participant data meta-analysis of the emerging cohorts is critical to assess both differential presentation and outcomes by underlying risk factors, and to determine the differential effects of interventions to reduce the rates of complications. With the establishment of several national and global prospective cohorts, we expect the sample size of our meta-analysis to increase further in the coming months. Our living systematic review and meta-analysis with its regular search and analyses updates is ideally placed to assess the impact of new findings on the rapidly growing evidence base.

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Contributors: JA and ES are joint first authors. ST, MB, and JA conceptualised the study. MY, SC, LD, TK, ACL, AD, DZ, RB, SL, XQ, and MYuan selected the studies. JA, ES, MY, LD, DZ, XQ, and MYuan extracted the data. JZ conducted the analyses. All coauthors contributed to the writing of the manuscript and approved the final version. ST, JA, ES, and JZ are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare:

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Ethical approval: Not required.

Data sharing: No additional data available.

The corresponding author (ST) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been disclosed.

Dissemination to participants and related patient and public communities: The PregCov-19 LSR Group will disseminate the findings through a dedicated website (www.birmingham.ac.uk/research/who-collaborating-centre/pregcov/index.aspx) and social media.

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Supplementary information: appendices 1-9

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